Clinical Trials

Section 2

Designs for Clinical Trials

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Overview of Presentation

- Types of Study Designs
- RCT Background
- RCT Design Elements
- Classification of Trials
- Types of Clinical Trial Designs

Types of Study Designs Descriptive

- Case Reports
- Case Series
- Cross-Sectional Surveys

Types of Study Designs Analytic-Observational

- Case-Control
  - Subjects with (cases) and without (controls) a disease (outcome) are selected to determine if a treatment (exposure) occurred in the past
- Cohort
  - Subjects with and without an exposure (treatment) are selected
  - Subjects are followed to determine if a disease (outcome) occurs

Types of Study Designs Intervention (Clinical Trial)

- A cohort study in which the investigator controls the assignment of subjects to the treatment (exposure)
- Subjects are followed and the treatment effect on a disease (outcome) is observed

Types of Study Designs Randomized Clinical Trial

- A RCT is an intervention study in which the treatment assignment is random rather than systematic

Advantages of a RCT

- A well-designed clinical trial provides the strongest evidence of any study design that a treatment causes a response
- Groups are as alike as possible except for the assigned treatment
- Precision is maximized
- Bias is minimized

The Basic 2 Group RCT

- Basis for differences between responses of the two groups
  - Sampling variation or chance
  - Inherent differences between the two groups
  - Differences in handling and evaluation during follow-up
  - The true treatment effect

- Minimizing likelihood that treatment difference is due to sampling variation or chance
  - accept small significance level (p value) for statistical tests
  - P=.01: there is a 1 in 100 probability that the difference observed is due to chance

- Minimizing likelihood that treatment difference is due to inherent differences between the two groups
  - Randomization
  - Stratification of the randomization

- Minimizing likelihood that treatment difference is due to differences in handling and evaluation during follow-up
  - Blinding
  - Maximizing compliance with treatment
  - Minimizing withdrawals from study

- When these potential causes are well controlled, the only possible explanation left for the observed difference:

- There truly is a treatment difference

Randomization

- Each study participant has the same chance of receiving each of the treatments
- Probability of one patient being assigned a particular treatment is independent of the probability of any other patient being assigned that treatment
- Haphazard does not equal random

Randomization (continued)

- Advantages
  - Eliminates treatment selection bias
  - Tends to create groups that are comparable for all factors that influence outcome, known or unknown
  - Gives validity to the statistical tests
- Disadvantage
  - Randomization does not guarantee comparable groups
  - Any baseline differences that exist are attribute to chance rather than bias

Blocked Randomization

- It is possible for all participants to be assigned to one treatment by chance
- Blocked randomization makes sure group sizes are equal by stopping assignment to a group once it reaches a preassigned level
- Balance at end of the study
- Balance at interim time points
- Permuted blocks: randomly change the pattern from one block to the next
- Random block sizes

Stratification (of the Randomization)

- Forces balance
- Randomize within strata to control for important prognostic factors that may be imbalanced between treatment arms
- Always stratify on center to control for variability among sites
- Usually don't stratify on more than 2 or 3 factors
- Generally not necessary for trials larger than 200 patients
- The larger the trial, the more likely randomization will produce comparable groups
- Always control for stratification in the analysis - improves efficiency

GAIT (Glucosamine/Chondroitin Arthritis Intervention Trial)

- 5 treatment groups
  - Glucosamine
  - Chondroitin
  - Combination
  - Celecoxib
  - Placebo
- Group sizes are equal
- Stratification factor
  - Baseline Pain score (low moderate, high moderate)
  - Participating Site

GAIT (Glucosamine/Chondroitin Arthritis Intervention Trial)

- Treatment masking
  - Two bottles of tablets given
    - G, C, G+C or placebo
    - Celecoxib or placebo
- Randomizations are blocked after every 10 assignments within each stratum combination
- Randomization blocks are permuted

Problems After Randomization

- Differences between groups can creep in during follow-up
- Can only be minimized but not totally eliminated
  - Biased evaluation
  - Treatment noncompliance
  - Withdrawals from study

Masking (Blinding)

- Concealing the identity of the treatments
- Eliminates effect of biases towards the treatments
- Blinding the patient (single-blind)
- Also blinding the investigator (double-blind)

Impediments to Masking

- Medication Trials
  - Side effects
  - Inability to make medications identical in appearance
- Surgery trials
  - Rarely is the patient or investigator masked
- Trials comparing two very different treatment modalities
  - Surgery vs medication
  - Surgery vs no surgery

Blinding Strategies

- If the response is objectively measured, less concern
- Matching placebo
- Sham surgery (usually not ethical)
- Independent blinded evaluator
- Not sharing treatment outcomes data with investigators until after all data are collected

Withdrawals From Study

- Increases with:
  - length of follow-up
  - adverse events
  - lack of effect
- Reduce sample size and statistical power
- Difficult to assess how withdrawals affect treatment comparisons

Withdrawal Bias

- Withdrawal rate differences between groups
  - Did the treatment cause the withdrawal?
  - Reduces comparability of the randomized groups
  - Less data in one group
- Large but equal withdrawal rate
  - Are characteristics of withdrawn patients different from those who remain in study?

Follow-up Strategies

- Attempt to follow up all randomized patients, even if they are noncompliant
- Aggressively try to prevent losses to follow-up and withdrawals of consent
- Accept few reasons to withdraw
  - Death
  - Withdrawal of consent
  - Loss to follow-up

VA CSP #246 TURP vs WW for BPH -1

- Participants with moderately symptomatic BPH randomly assigned to undergo TURP or watchful waiting
- 10% refused TURP after randomization
- 25% eventually crossed over to TURP from WW

VA CSP #246
TURP vs WW for BPH - 2

- TURP refusals had lower level of symptoms at baseline than others
- Crossovers to TURP had higher level of symptoms at baseline
- If analysis was restricted to those who stayed with the assigned treatment, the TURP group would have started out with more symptoms than the WW group

VA CSP #246
TURP vs WW for BPH - 3

- If analysis was according to the treatment received, the TURP group also would have started out with more symptoms than the WW group
- Intention to treat: analyze according to the original assignment. The only analysis where the treatment groups are comparable at baseline

VA CSP #246
TURP vs WW for BPH - 4

- Analysis done all 3 ways
- TURP was superior to WW regardless of the analysis
- NEJM published only the intent to treat analysis
- Side note: Large % of WW patients did well. That was the result that received the most press.

Classification of RCT's

- Phase I - safety and dosing
- Phase II - limited efficacy
- Phase III - efficacy / effectiveness
- Phase IV - post marketing surveillance
  - Safety when given to large numbers of patients

Common Types of RCT Designs

- Parallel group
- Factorial
- Equivalence
- Crossover
- Large, simple
- Cluster/community designs

Parallel Group

- Most typical design
- Usual design for drug trials
- Randomize to one of 2 or more treatment groups and follow patients over time
  - 2 treatment arms most common, i.e. - drug vs. placebo

Parallel Group

Multiple treatment arms

- Advantages
  - test more than one treatment/dose with a single control group
  - compare multiple treatments/doses in one trial
- Disadvantage
  - Increases sample size - Type-I error correction for multiple comparisons

VA Cooperative Study #290
Monotherapy of Hypertension

- Which type of antihypertensive medication is most effective in controlling blood pressure
- 7 Treatment Groups!
  - Diuretic (hydrochlorothiazide)
  - Beta Blocker (prazosin)
  - ACE Inhibitor (captropril)
  - Calcium Channel Blocker (diltiazem)
  - Alpha Blocker (prazosin)
  - Central Alpha 2 agonist (clonidine)
  - Placebo

VA Cooperative Study #290
Complexity Upon Complexity

- Phase A
  - -randomize to one of 7 treatments
- Phase B
  - -if phase A treatment was not effective, rerandomize to one of the 6 other treatments
- Phase C
  - If phase B treatment was not effective, add the original phase A treatment
  - 15 treatment combinations (placebo not included)

Factorial

- Evaluate treatments given singly and in combination
- Ideally involves treatments that don't interact with each other
- Endpoints or disease can be the same or different

Factorial Trials

Advantages

- Test 2 or more hypotheses in 1 experiment
- Allows for an exploratory analysis of the effect of combination therapy
  - very important if combination therapy is likely
  - If study of interaction important, a large sample size is required
- Increased acceptability by patients
  - 2 x 2 factorial - only 1/4 receive placebo

Disadvantages

- A negative interaction - loss of power
- A significant interaction - tremendous loss of power - 1/2 the sample size

Examples of Factorial Trials

Physicians' Health Study

- 2x2 factorial to determine whether:
  - low dose aspirin decreases CV events
  - vitamins reduce incidence of cancer
  - no interaction expected
  - endpoints different for each treatment

CSP #484 - Heart Failure -PSF Trial

- 2x2 factorial to determine whether:
  - a beta-blocker and/or an ARB reduces all-cause mortality + CV hospitalization
  - possible treatment interaction
  - same endpoint for both treatments

2 x 2 Factorial

- Most common factorial design
- For two treatments, A and B, patients assigned to one of 4 treatment groups
  - A alone
  - B alone
  - Both A + B
  - Neither A nor B
- GAIT study
  - 2 X 2 factorial with an active comparator
    - G, C, G+C, placebo, celecoxib

2 x 2 Factorial

Drug A	Drug B: No	Drug B: Yes
No	A-B-	A-B+
Yes	A+B-	A+B+

Marginal or Main Effect

Drug A	Drug B: No	Drug B: Yes	
No	A-B-	A-B+	A-
Yes	A+B-	A+B+	A+
	B-	B+	

Treatment Interaction

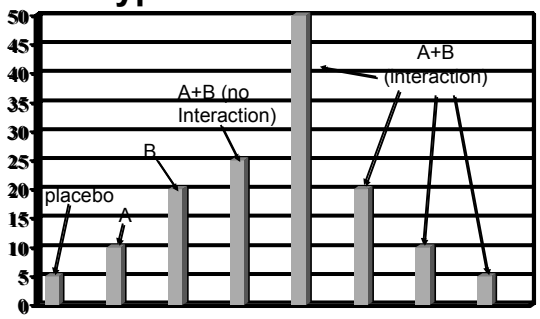
No interaction

- Effect of treatment A is not influenced by B and vice versa
  - Example - both A and B when given alone increase QOL by 10 points and in combination they increase it by 20 points

Interaction

- Effect of the treatment combination is different than the effect of either treatment given alone (interaction can be negative or positive)
  - Example of a negative interaction - A and B in combination improve QOL by only 15 points
  - Example of a positive interaction - A and B in combination improve QOL by 25 points

Types of Interactions



Equivalence Trials

- Active Control Equivalence Study
- Show therapies same within a certain tolerance
- Typically used to evaluate if a therapy is equivalent to the standard treatment but with a lower side effect profile or lower cost
  - cancer treatments
  - antibiotics

Equivalence Trials

- Setting tolerance limit can be difficult
  - How to define equivalent
  - Often set too high because of sample size
- Equivalence studies require large sample sizes to rule out small differences
  - smaller the difference the larger the study
- The use of confidence intervals is the preferred method of analysis

VA SCCOPE Trial

- Show not giving steroids equivalent to giving steroids for COPD
- Endpoint = treatment failure
- Powered to detect placebo no worse than steroids by 7.5%
  - Placebo – steroid < 7.5%
- Large criterion for equivalence
- Study showed placebo was not statistically significantly equivalent or steroids efficacious
- Points out problem with equivalence designs

Crossover Designs

- Each patient receives all treatments in different time periods with a washout period in between
- Randomize order of treatments: AB, BA
- Efficient if no carryover effects from one time period to the other
  - Problem with drugs
- Yield smaller sample sizes because each subject serves as own control
- Rare but sometimes used for psychiatric studies or phase -I drug trials for dosing

VA CSP #418
Hearing Aid Trial

- 3 period, 3 treatment crossover design
- Studied 3 types of hearing aids (ABC)
- Don't expect carryover effects
- Subjects randomized to one of six possible sequences of hearing aids
  - ABC
  - ACB
  - BAC
  - BCA
  - CAB
  - CBA

Large, Simple Trials

- European/Canadian approach
- Answer important question quickly and/or definitively
- Hard endpoints - no central review
- Small/moderate treatment effects
- Enroll large numbers of patients
- Little data collection/QC
- Pragmatic - difficult to study mechanisms
- Physician's Health Study

Cluster Designs

- Use when its more practical or necessary to administer treatments to groups of patients
  - Clinics
  - Communities
- CSP #470 - Gulf War EBT Trial, CBT administered to groups
  - Unit of analysis is the group not patient
- CSP #704 - Informed consent sub-study, VAMC randomized to consent document
  - Unit of analysis is the hospital not patient